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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EDWARDS ANELI, PALMER & DODGE LLP			ARNOLD, ERNST V	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/516,418	Applicant(s) BOUVIER ET AL.
	Examiner ERNST V. ARNOLD	Art Unit 1616

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If no period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 03 November 2008.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1,3-5,7-9,11-33, 65, 113, 117, and 123 is/are pending in the application.
- 4a) Of the above claim(s) 31,32,65,113 and 117 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1,3-5,7-9,11-30,33 and 123 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO/SB/08)
 Paper No(s)/Mail Date _____
- 4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date _____
- 5) Notice of Informal Patent Application
- 6) Other: _____

DETAILED ACTION

Claims 31, 32, 65, 113 and 117 are withdrawn. Claims 1, 3-5, 7-9, 11-30, 33 and 123 are under examination.

Applicant's amendments have necessitated a new ground of rejection. Accordingly, this Action is Final.

Withdrawn rejections:

Applicant's amendments and arguments filed 11/3/08 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed below is herein withdrawn. Claims 1, 3-5, 7-9, 11, 20-30, 33 and 123 were rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al. (WO 00/70334). The Examiner is withdrawing this rejection because a chemical alteration of a biomolecule selected from alkylation and reduction are not verbatim disclosed by Lee et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

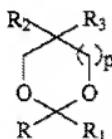
Claims 1, 3-5, 7-9, 11-30, 33 and 123 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (WO 00/70334) in view of Zee-Yong et al. (Anal Chem. 2001, 73, 2558-2564) and Nelson (US 6,093,541).

Applicant claims a method for enhancing a chemical digestion, chemical alteration or a combination thereof of a biomolecule comprising contacting the molecule with a surfactant.

Determination of the scope and content of the prior art

(MPEP 2141.01)

27. A method of solubilizing a substance comprising contacting a substance with a surfactant represented by the formula (Formula I):



in which

p is 0, 1 or 2;

R is alkyl;

R₁ and R₂ are each, independently, hydrogen or methyl; and

R₃ is selected from -OSO₃⁻, -R₄OSO₃⁻, -R₄OR₅SO₃⁻, and -OR₅SO₃⁻,
wherein R₄ and R₅ are each, independently, lower alkyl.

It is the Examiner's position that "solubilizing a substance" reads on "enhancing a chemical reaction of a molecule" and is a favorable chemical property with increased efficiency of instant claims 20 and 21. Instant claim 25 is taught when R₂ = H and p = 0. Instant claim 26 is obvious when p = 1, R₂ = H, R₃ = -OR₅SO₃⁻, R = alkyl and R₁ is methyl (Page 12, Scheme 1). Instant claim 27 is taught when p = 0, R₁ = methyl, R = alkyl, R₂ = H and R₃ = -R₄OSO₃⁻ (Page 12, Scheme 1). Lee et al. teach wherein the substance is an inclusion body, lipophilic protein or membrane-bound protein sample (Claims 28-31). Lee et al. teach a method where a proteolytic protein (lysozyme, trypsinogen, pepsin, for example) is contacted with ALS-I thus reading on instant claims 2, 6 and 7 (page 14, lines 5-15). The presence of a biomolecule in the aqueous surfactant solution makes it a biological sample and reads on instant claim 4. The aqueous

surfactant solution has water, which is a biological fluid and reads on instant claim 5. Samples were heated to ensure protein denaturation and anticipates instant claim 22 (page 14, lines 14-15). Gels were run in the absence of SDS thus reading on instant claim 30 and 33 (page 14, lines 26-31). Lee et al. teach 50 μ L aliquots and thus perform under microscale conditions and reads on instant claim 29. Mass spectrometry was used for detection of myoglobin treated with ALS-I thus reading on instant claims 3, 8 and 28 (page 15, lines 4-22). Lee et al. state that "mass spectrometric detection" refers to Matrix Assisted Laser Desorption Ionization MALDI which applicant states on page 21 lines 21-22 is surface desorption ionization analysis and reads on instant claim 9 (Page 6, lines 30-32). Gels run with ALS-I were stained with zinc-imidazole (page 14, lines 26-31). On one hand, the surfactant was degraded in glacial acetic acid for 16 prior to mixing with myoglobin and on the other hand trifluoroacetic acid was added to degrade the surfactant before electrospray mass spectrometry of myoglobin and reads on claims 11, 23, 24 and 123 (page 15, lines 10-22; page 16, line 8 and page 18, lines 14-26).

Zee-Yong et al. teach identification of individual proteins (11 proteins were studied and include: rabbit phosphorylase, bovine serum albumin, chicken egg ovalbumin, rabbit aldolase, bovine carbonic anhydrase, horse myoglobin, bovine hemoglobin, horse cytochrome c, chicken egg lysozyme, and bovine ubiquitin (Page 2559 Experimental section).) in complex protein mixtures by MALDI mass spectrometry (Abstract). Thermal denaturation followed by in-solution trypsin digestion is used to achieve uniform digestion of the constituents of the protein mixture (Abstract and page 2559, experimental section). **Reduction** of disulfide bonds with dithiothreitol is taught (page 2559, right column).

Nelson teaches proteases for use in mass spectrometers (Abstract and column 7, lines 28-65 and claim 4). Nelson teaches chymotrypsin, Glu-C, Lys-C, S. aureus V8 protease, clostripain, and trypsin, for example, as enzyme proteases and chemical agents such as cyanogens bromide and hydroxylamine (column 7, lines 28-65). Nelson teaches immobilized proteases (Figures 3, 3A, 5 and 6; and column 16, example 10 for example). Nelson teaches adding **reducing agents** (column 7, lines 55-57).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. Lee et al. do not expressly teach a method wherein the reaction comprises chemical digestion/chemical alteration wherein the chemical alteration is selected from the group consisting of alkylation, reduction and a combination thereof and wherein the biomolecule is contacted with a protease; that is immobilized. This deficiency in Lee et al. is cured by the teachings of Nelson et al. and Zee-Yong et al.

2. Lee et al. do not expressly teach a method wherein the method further comprises separating the resulting biomolecule fragments. This deficiency in Lee et al. is cured by the teachings of Zee-Yong et al.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to perform chemical digestion/chemical alteration is selected from the group consisting of alkylation, reduction and a combination thereof or contact the biomolecule with a

protease that is immobilized, as suggested by Zee-Yong et al. and Nelson, in the method of Lee et al. and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Zee-Yong et al. and Nelson teach common reagents and techniques known to one of ordinary skill in the art used in the analysis of proteins using mass spectroscopy which include reduction.

2. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to separate the biomolecule fragments after contacting the biomolecule with a protease, CNBr or hydroxylamine and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because after the chemical digestion, the fragments would be run on the mass spectrometer and separated for identification as generally taught by Nelson et al. and Zee-Yong et al.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976).

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to arguments:

Applicant asserts that nothing in the cited references suggests the instantly claimed method and that there is no overlap between the prior art and the instantly pending claims. Respectfully the Examiner cannot agree for the following reasons.

Fact #1: The instantly claimed compounds are known for use in solubilizing denatured proteins for various spectroscopic techniques as taught by Lee et al. and furthermore Lee et al. teach other equivalents can be recognized by routine experimentation (page 21, lines 8-12).

Fact #2: Zee-Yong et al. establish that it is known to denature protein before digestion (page 2559, right column). Further Zee-Yong et al. establish that digestion is a common procedure to perform on proteins before spectrometric analysis.

Fact #3: MPEP 2141.03 states (in part), “A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton.” *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 167 LEd2d 705, 82 USPQ2d 1385, 1397 (2007). “[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle.” *Id.* Office personnel may also take into account “the inferences and creative steps that a person of ordinary skill in the art would employ.” *Id.* At 1396, 82 USPQ2d at 1396. The hypothetical person having ordinary skill in the art to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art.” *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (Examiner added emphasis).

It is on the basis of these facts that the Examiner arrives at the conclusion that the instantly claimed method would have been obvious to one of ordinary skill in the art at the time

of the invention. There is no teaching in the art that expressly states that one cannot digest proteins after treating the protein with a surfactant to assist solubilization or that the surfactant as taught by Lee et al. cannot be used on protein fragments. The concept remains the same whether one is using the surfactants to enhance the solubility of denatured proteins or fragments of protein. It is known that solubilization of proteins works. It is known that digestion of proteins works. It is merely ordinary creativity to combine the two concepts. One of ordinary skill in the art would expect solubilized proteins to be digested/alkylated/reduced in the presence of the proper agents. The expected result remains the same and there has is nothing on the record to suggest otherwise. In fact, it appears to be desirable to use the method of Lee et al. because Lee et al. teach that the sensitivity of mass spectrometric detection of denatured proteins in the presence of degraded ALS is much greater than the presence of SDS (page 11, lines 20-21).

Applicant's arguments are not persuasive and the rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting

ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-5, 7, 22, 23, and 25-27 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 3, 5-7, 16, 18 and 27 of copending Application No. 10/169,002 (Now US 7,229,539). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant method of enhancing a chemical reaction of a molecule comprising contacting the molecule with a surfactant is encompassed by the patented claims drawn to a method for performing electrophoresis comprising contacting a sample with the same surfactant as instantly claimed as well as the method of solubilizing a substance comprising contacting the substance with the same surfactant as instantly claimed (patented claims 1 and 27). Patented claim 27 recites inclusion bodies, lipophilic proteins, receptors, membrane bound proteins and biological tissues which reads on instant claims 2, 4-7. Patented claim 18 is drawn to mass spectrometric detection. Patented claims 2 and 3 recite degrading the surfactant by contacting it with an acidic solution which reads on instant claims 23 and 24. The surfactants in patented claims 1, 5-7 and 27 read on instant surfactants in claims 1 and 25-27. One of ordinary skill in the art would have recognized the obvious variation between the instant invention and the copending application because the subject matter of the instant invention embraces or is embraced by the patented claims.

Response to arguments:

Applicant stated that the rejection would be addressed once allowable subject matter was indicated. Until that time, the claims remain rejected.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ernst V. Arnold whose telephone number is 571-272-8509. The examiner can normally be reached on M-F (6:15 am-3:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Ernst V Arnold/

Examiner, Art Unit 1616